Medical Mycology Case Reports 47 (2025) 100690

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Pulmonary coccidioidomycosis presenting as a fungal ball mimicking aspergilloma

Rik van den Biggelaar [a,1], Tristan Couwenbergh [a], Alexander C.A.P. Leenders [b], C.A. van der Sloot [c], Henrich van der Lee [a], Jochem B. Buil [a,*]

[a] Department of Medical Microbiology, Radboud University Medical Centre, Nijmegen, the Netherlands
[b] Department of Medical Microbiology, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands
[c] Department of Pulmonary Diseases, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands

ARTICLE INFO

Handling Editor: Dr Adilia Warris

Keywords:
Coccidioidomycosis
Mycetoma
Fungal ball
pulmonary cavitation

ABSTRACT

A 49-year old female, known to have had an asymptomatic pulmonary cavity since 2015, presented in 2023 with hemoptysis. Radiology showed a mass suspected to be an aspergilloma. Due to persistent hemoptysis, lobectomy was performed. Pathological examination revealed fungal hyphae, and the cultured fungus was identified as a Coccidioides species by LSU sequencing. Microscopy, culture, and ITS sequencing at the national reference center confirmed the identification of Coccidioides posadasii. The patient's last visit to an endemic region was 13 years before the symptomatic disease.

1. Introduction

Coccidioidomycosis, also known as Valley Fever, is caused by the dimorphic fungi *Coccidioides immitis* and *C. posadasii*. The fungi are found in arid desert soil. *C. immitis* is primarily found in California with the Southern Arizona and the San Joaquin Valley region accounting for 95 % of USA cases, whereas *C. posadasii* is primarily found in the southwestern region of the USA, in Mexico, and in arid regions of South America [1]. During the rainy season, *Coccidioides* species grow rapidly as mycelia in the soil. Subsequently, hyphal cells undergo alternating autolysis to form barrel-shaped spores called arthroconidia, which remain viable for many years [2]. When the soil is disturbed, arthroconidia can become airborne, ready to be inhaled.

Occupations associated with soil-disruptive activities, such as construction and agricultural workers, are especially at risk [3]. Additionally, prison inmates in the San Joaquin Valley are at increased risk, leading to a policy of excluding inmates with nonreactive coccidioidomycosis skin tests from these facilities [4].

Once inside the body, arthroconidia transform into spherules containing endospores. Symptoms usually occur 1–3 weeks after exposure to the arthroconidia. Coccidioidomycosis is often subclinical or presents as a mild and self-limiting pneumonia; however, dissemination has been described in 0.5–2% of cases, most often in immunosuppressed and African American or Filipino ethnicities [2]. Once exposed to *Coccidioides*, latent infection or reactivation can occur months to years later if a patient becomes immunocompromised [5].

We report a case of an immunocompetent 49-year old Dutch female with pulmonary coccidioidomycosis presenting with a pulmonary cavity and fungal ball mimicking aspergilloma years after traveling to an endemic region. Although spherules are the predominant form of this dimorphic fungus within the body, this case exemplifies that microscopy showing hyphal forms does not exclude coccidioidomycosis.

2. Case presentation

A 49-year old female presented in October 2023 with significant hemoptysis and was later admitted to having sporadic hemoptysis for 2 years. The patient was diagnosed with a pulmonary cavity in 2015, discovered as an incidental finding. Because the cavity was asymptomatic, and subsequent chest computed tomography (CT) scans did not show any change over time, no further follow-up was deemed necessary.

Radiological evaluation by chest CT showed expansion of the pre-existing cavity and formation of a mass [Fig. 1]. Positron emission tomography/computed tomography (PET/CT) showed PET avidity of the mass. Because malignancy had not been excluded, a CT-guided biopsy was planned. However, during the subsequent chest CT the mass

* Corresponding author.
E-mail address: jochem.buil@radboudumc.nl (J.B. Buil).
[1] Present address: Department of Medical Microbiology, Eurofins PAMM, Veldhoven, the Netherlands.

https://doi.org/10.1016/j.mmcr.2024.100690
Received 26 June 2024; Received in revised form 6 December 2024; Accepted 11 December 2024
Available online 12 December 2024

displayed mobility and was highly suspected of aspergilloma, and therefore it was decided to not perform the biopsy.

Laboratory analysis did not show any eosinophilia, and *Aspergillus* IgG antibodies were negative. Bronchoalveolar lavage (BAL) was performed, and the cultures did not contain any fungi, bacteria, or mycobacteria. No *Aspergillus* galactomannan antigen test could be performed on the BAL because of insufficient material; however, the galactomannan lateral flow assay (TECO® Fast, Biognost) on sputum was positive (0.72, cutoff 0.5).

Because of the persistence of hemoptysis and suspicion of aspergilloma, a multidisciplinary team decided to perform a lobectomy after pre-treatment with voriconazole 2dd 200 mg for 2 weeks. After the surgery, voriconazole was continued only shortly for an additional 2 weeks as the lesion was resected completely without suspicion spillage of fungal elements into the pleural space, and long term adjuvant antifungal therapy was not deemed necessary [6]. Pathological examination of the lung tissue showed an abundance of uniform thin hyphae in the Grocott stain, which supported the suspicion of aspergilloma [Fig. 2]. Fungal growth was observed 3 days after inoculation on Sabouraud dextrose agar. Microscopy of the fungal colonies on days 3 and 8 showed no characteristic features required for identification. Subsequent sequencing of the large ribosomal subunit (LSU) identified the fungus as a *Coccidioides* species. *Coccidioides* serology using a lateral flow assay (LFA) was negative. Travel history within endemic regions included Brazil (1997 and 2005), Mexico (1999), Costa Rica (2001), Cuba (2004) and a 6 month stay in Honduras (2007–2008). During her stay, the patient also traveled to Guatemala and Belize.

The tissue sample and extracted DNA were sent to the national reference center for identification and susceptibility testing. As the large subunit (LSU) rDNA regions are highly conserved in *Coccidioides* it only allows recognition at the genus level [7]. Phylogenetic analysis of the internal transcribed spacer (ITS) sequence was consistent with *Coccidioides posadasii* [Fig. 3]. Blankophor staining of the lung tissue showed hyphae and spherules [Fig. 4], and the fungal culture on Sabouraud Dextrose Agar (SDA) was positive for *Coccidioides* [Fig. 5]. *Aspergillus* PCR of the lung tissue was negative, excluding co-infection. Unfortunately, the isolated fungus failed to sporulate, which prevented antifungal susceptibility testing.

Our multidisciplinary team decided to treat the chronic coccidioidomycosis with fluconazole 1dd 400 mg for 3 months postoperatively. Disease activity was subsequently evaluated using a chest CT scan at 3 months, which did not reveal evidence of disease activity. At the 6-month follow-up, the patient remained clinically stable without observable signs of disease activity. Given the absence of comorbidities and the presence of a single, stable lesion that had persisted for several years without dissemination, further immunological analysis was not deemed necessary at that time. In case of disease progression or insufficient clinical response further immunological testing would be performed. No laboratory personnel were determined to have been exposed to high concentrations of arthrospores after risk assessment.

3. Discussion

Coccidioides is non-endemic to the Netherlands, and coccidioidomycosis cases are very rare [8]. Diagnosis may be delayed or missed because of the low index of suspicion. A further complicating factor in this case was the atypical manifestation of a fungal ball and hyphal forms during pathological examination, as the patient was presumptively treated for aspergilloma. This exemplifies that physicians must keep coccidioidomycosis in mind when evaluating patients who have traveled to endemic areas.

The hyphal growth of *Coccidioides* within the body was first described by Forbus et al. in a review of 95 patients with disseminated coccidioidomycosis [9]. Early reviews by Pucket et al. and Forsee et al. reported the presence of hyphae in pulmonary cavities in 25/34 (73 %) and 15/30 (50 %) of patients, respectively, compared to 9/30 (30 %) and 2/20 (10 %) of patients with pulmonary granulomas [10,11]. This is in stark contrast to the following 7 decades, when this phenomenon has only been sporadically reported. Coccidioidal hyphae have also been described in the cerebrospinal fluid in 8 cases associated with intracranial foreign bodies [12] and 2 cases of cutaneous disease [13,14].

It is estimated that 60 % of infections are asymptomatic [2]. Patients with symptomatic pulmonary coccidioidomycosis usually have dense infiltrates, often in the upper lobe, with associated hilar or mediastinal adenopathy. Severe disease is uncommon and presents mostly in patients with high inoculum exposure and immunocompromised patients. In these patients, pulmonary infection may manifest as diffuse infiltrates or miliary disease [1,2]. In some patients, coccidioidal pneumonia will not completely resolve, and a solitary nodule (90 % of cases) will persist in the peripheral lung parenchyma. Typically, these nodules are benign and do not cause any symptoms [1,15]. Thin-walled cavities may also develop, with half of them closing within 2 years. A small portion of

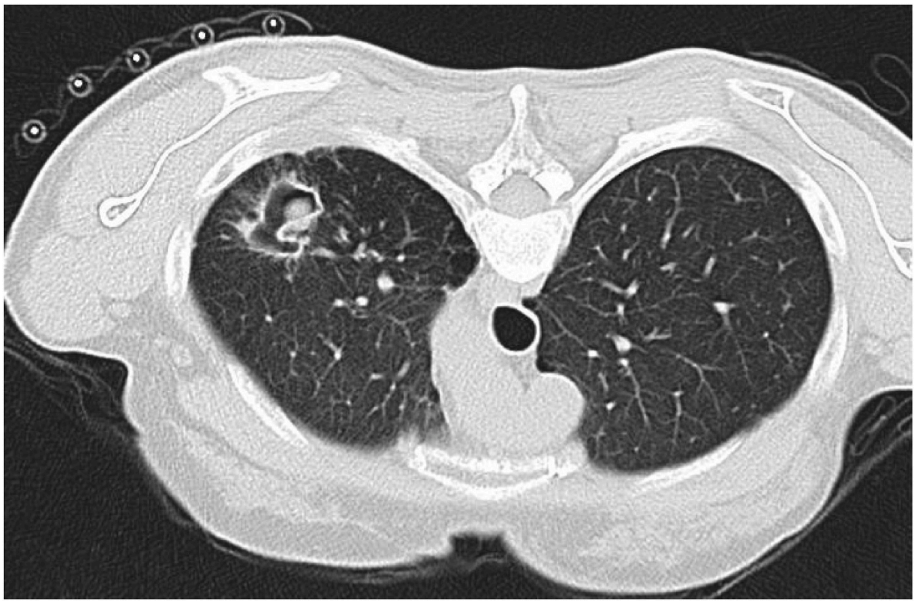

Fig. 1. Chest CT showing a mass in the pulmonary cavity.

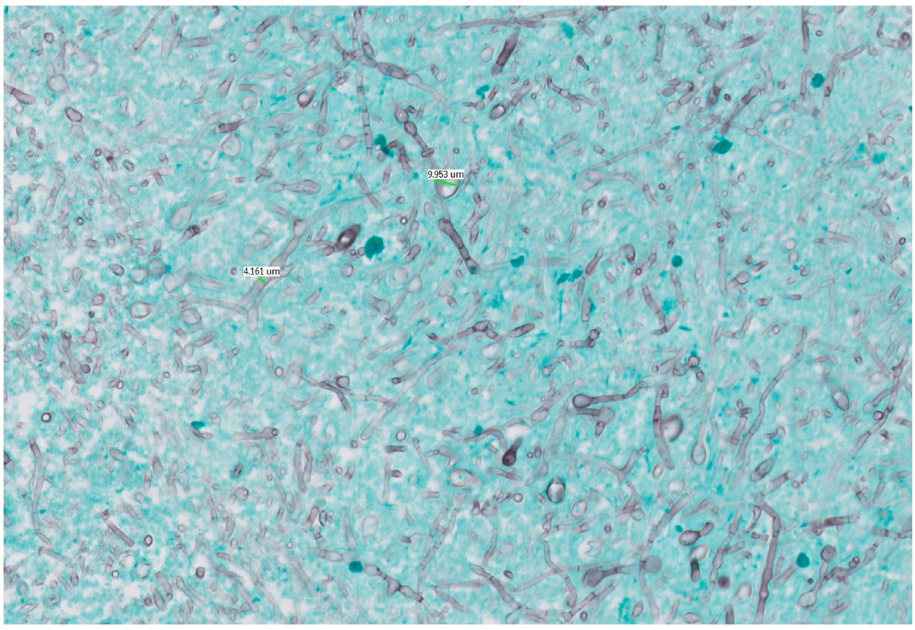

Fig. 2. Grocott staining of lung tissue showing an abundance of hyphae.

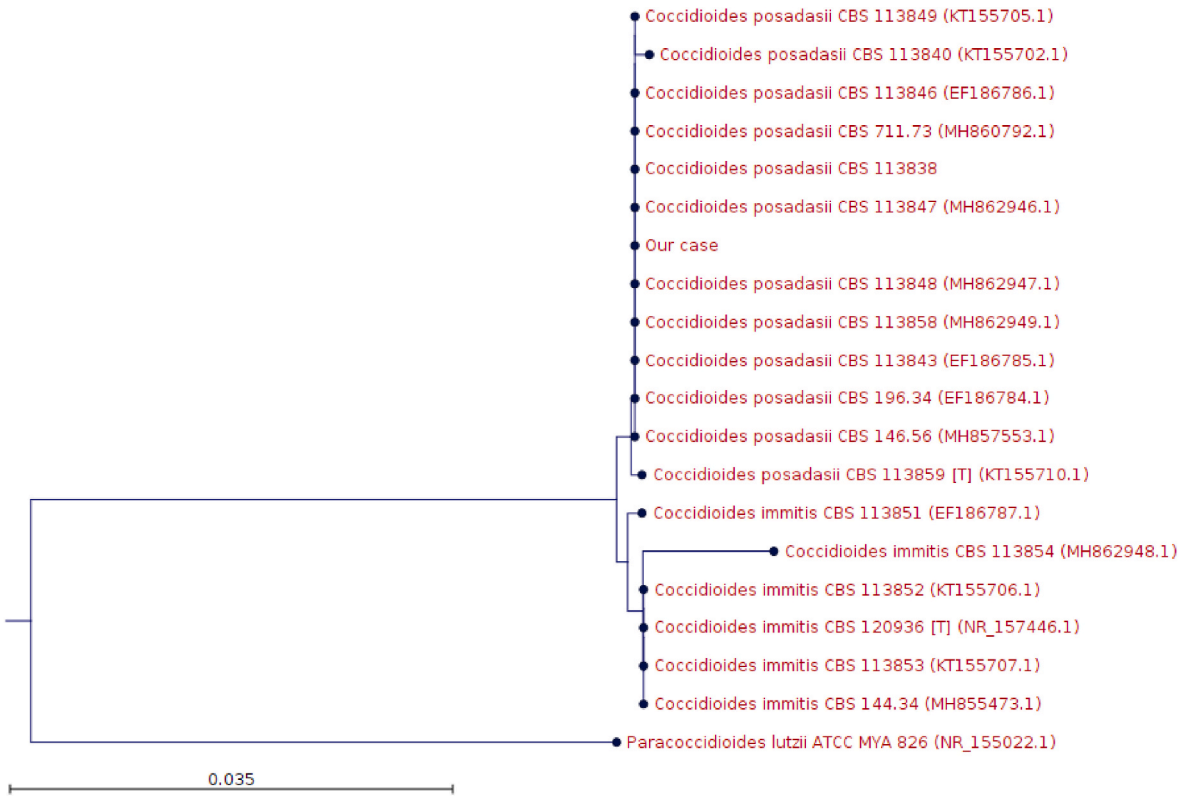

Fig. 3. Phylogenetic tree based on ITS of *Coccidioides immitis* and *C. posadasii*. *Paracoccidioides lutzii* was used as the outgroup.

cavities can persist for more than 10 years [15]. Cavitary disease may also be complicated by the development of a fungal ball caused by other fungi, such as *Aspergillus* species or by *Coccidioides* itself, as exemplified by our case [1].

No clinical trials have been conducted to determine the optimal drug, dose, or duration of treatment for pulmonary coccidioidomycosis. In cases of uncomplicated pneumonia in patients not at risk for dissemination, the disease is typically self-resolving and does not require antifungal therapy. In addition, the presence of an asymptomatic pulmonary nodule or cavity does not warrant antifungal therapy. However, symptomatic cavitary disease should be treated with fluconazole 400 mg daily (or itraconazole 200 mg orally twice daily), and surgical management should be considered [2]. Jaroszewski et al. suggest treating patients with clinically significant cavitary disease with postoperative antifungal therapy for at least 2–3 months [16].

In the United States, dimorphic fungi such as *Histoplasma capsulatum*,

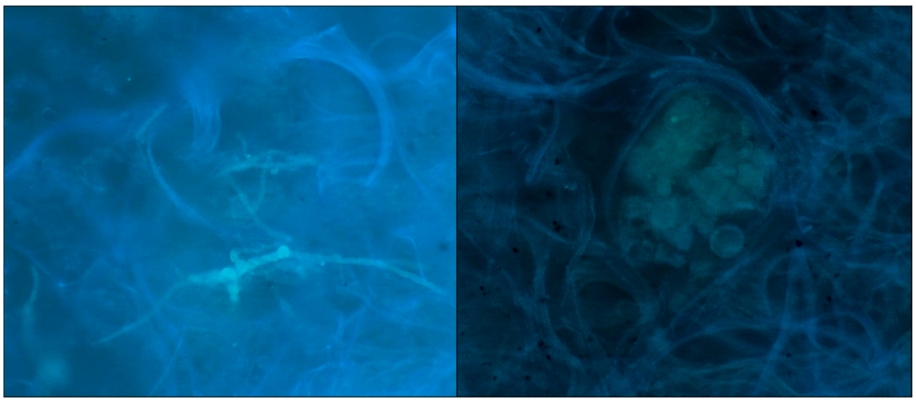

Fig. 4. Blankophor staining of lung tissue showing hyphae (left) and spherules (right).

Fig. 5. Fungal culture of *Coccidioides posadasii* on Sabouraud Dextrose Agar (left) and Sabouraud Dextrose Broth (right).

Blastomyces dermatitidis, and *Coccidioides* species are responsible for the majority of laboratory-acquired fungal infections. Although some cutaneous infections through inoculation have been documented, most laboratory-acquired infections are caused by the inhalation of arthroconidia from handling *Coccidioides* in the mold form [17]. Clinical materials with *Coccidioides* are generally considered to pose little infectious risk as its spherules cannot be inhaled [18]. However, as demonstrated in our case, hyphae and arthroconidia can be present in clinical materials.

Our case describes chronic pulmonary coccidioidomycosis presenting as a cavity with a fungal ball mimicking aspergilloma. The clinical presentation, combined with the presence of hyphae during histological examination, delayed the proper diagnosis and treatment. Furthermore, it could have led to the exposure of laboratory personnel to highly infectious arthroconidia of the cultured mold. This exemplifies that the presence of hyphae does not exclude coccidioidomycosis.

CRediT authorship contribution statement

Rik van den Biggelaar: Writing – original draft, Conceptualization. **Tristan Couwenbergh:** Writing – original draft, Conceptualization. **Alexander C.A.P. Leenders:** Writing – review & editing, Investigation. **C.A. van der Sloot:** Writing – original draft, Conceptualization. **Henrich van der Lee:** Writing – review & editing, Investigation, Conceptualization. **Jochem B. Buil:** Writing – review & editing, Conceptualization.

Conflict of interest

There are no conflicts of interest.

Acknowledgements

We thank our patient, who provided consent for the publication of this case and allowed us to take an extensive travel history.

References

[1] G.R. Thompson 3rd, T. Le, A. Chindamporn, C.A. Kauffman, A. Alastruey-Izquierdo, N.M. Ampel, et al., Global guideline for the diagnosis and management of the endemic mycoses: an initiative of the European confederation of medical Mycology in cooperation with the international society for human and animal Mycology, Lancet Infect. Dis. 21 (12) (2021) e364–e374.
[2] N.F. Crum, Coccidioidomycosis: a contemporary review, Infect. Dis. Ther. 11 (2) (2022) 713–742.
[3] S.A. McCurdy, C. Portillo-Silva, C.L. Sipan, H. Bang, K.W. Emery, Risk for coccidioidomycosis among hispanic farm workers, California, USA, 2018, Emerg. Infect. Dis. 26 (7) (2020) 1430–1437.
[4] C. Wheeler, K.D. Lucas, G. Derado, O. McCotter, R.S. Tharratt, T. Chiller, et al., Risk stratification with coccidioidal skin test to prevent Valley Fever among inmates, California, 2015, J. Correct. Health Care 24 (4) (2018) 342–351.
[5] J. Brown, K. Benedict, B.J. Park, G.R. Thompson, 3rd. Coccidioidomycosis: epidemiology, Clin. Epidemiol. 5 (2013) 185–197.
[6] D.W. Denning, J. Cadranel, C. Beigelman-Aubry, F. Ader, A. Chakrabarti, S. Blot, et al., Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management, Eur. Respir. J. 47 (1) (2016) 45–68.
[7] K. Tintelnot, G.S. De Hoog, E. Antweiler, H. Losert, M. Seibold, M.A. Brandt, et al., Taxonomic and diagnostic markers for identification of Coccidioides immitis and Coccidioides posadasii, Med. Mycol. 45 (5) (2007) 385–393.
[8] K. Korsten, J. Altenburg, M. Gittelbauer, P. van Hengel, R. Jansen, K. van Dijk, Coccidioidomycosis presenting years after returning from travel, Med Mycol Case Rep 43 (2024) 100623.
[9] W.D. Forbus, A.M. Bestebreurtje, Coccidioidomycosis; a study of 95 cases of the disseminated type with special reference to the pathogenesis of the disease, Mil Surg 99 (5) (1946) 653–719.
[10] T.F. Puckett, Hyphae of Coccidioides immitis in tissues of the human host, Am Rev Tuberc 70 (2) (1954) 320–327.
[11] J.H. Forsee, R.B. Perkins, Focalized pulmonary coccidioidomycosis; a surgical disease, J. Am. Med. Assoc. 155 (14) (1954) 1223–1227.
[12] J. Shi, M. Wong, Y. Xu, Coccidioidal meningitis with hyphal forms detected in cerebrospinal fluid in a patient with ventriculoperitoneal shunt: a case report, J. Cent. Nerv. Syst. Dis. 13 (2021) 11795735211053446.
[13] R. Shahab, N.K. Amra, R. Rabah, J. Saunar, J. Soriano, J.A. Al-Tawfiq, Recurrence of cutaneous coccidioidomycosis 6 years after valley fever: a case presentation and literature review, Diagn. Microbiol. Infect. Dis. 89 (3) (2017) 218–221.
[14] A. Bonifaz, A. Tirado-Sanchez, G.M. Gonzalez, Cutaneous coccidioidomycosis with tissue arthroconidia, Am. J. Trop. Med. Hyg. 100 (4) (2019) 772.

[15] C.E. Smith, R.R. Beard, M.T. Saito, Pathogenesis of coccidioidomycosis with special reference to pulmonary cavitation, Ann. Intern. Med. 29 (4) (1948) 623–655.
[16] D.E. Jaroszewski, W.J. Halabi, J.E. Blair, B.J. Coakley, R.K. Wong, J.M. Parish, et al., Surgery for pulmonary coccidioidomycosis: a 10-year experience, Ann. Thorac. Surg. 88 (6) (2009) 1765–1772.
[17] K. Singh, Laboratory-acquired infections, Clin. Infect. Dis. 49 (1) (2009) 142–147.
[18] L. Porte, F. Valdivieso, D. Wilmes, P. Gaete, M.C. Diaz, L. Thompson, et al., Laboratory exposure to Coccidioides: lessons learnt in a non-endemic country, J. Hosp. Infect. 102 (4) (2019) 461–464.